Remarks

Telephone Interview

Applicants' undersigned attorney and Examiner Arnold conducted a telephonic interview addressing issues in the application on Tuesday, March 16, 2010. In the Official Action of December 28, 2009, Examiner Arnold suggested an interview prior to applicants' submission of a response to discuss potentially allowable subject matter and issues to be resolved including support for various features of the claims. At the conclusion of the interview, it was the undersigned attorney's impression that all issues were essentially resolved. The Examiner's Summary dated March 23, 2010 has been reviewed and is believed to be accurate. Each of the issues mentioned in the Summary are believed to be addressed consistent with the discussion.

The courtesy extended to applicants' attorney and examiner's professional suggestions are gratefully acknowledged.

Claims

Claims 5-8 remain in this application and have been amended to conform to the specification as filed and to the requirements of 35 USC 112. As discussed at the interview, the current amendments are respectfully submitted to obviate the examiner's grounds of rejection of claims 5 and 7 and overcome the objections to claims 5, 6 and 8. All claims as amended are supported in the originally filed application. More specifically, the claims have been amended and are supported as follows:

Claim 5 is amended to add a period at the end as required.

Claim 5 is amended further to add the statement "resulting in a shorter course of treatment and less side effects" as described at page 1 of the specification under "Disclosure of the Invention" and as evidenced by the Supplemental Declaration under Rule 1.132.

Claims 5 is further amended to recite the composition "consisting of" the recited active ingredients including artemisinin, primaquine and primaraquine in place of "consisting essentially of." The claim is further amended to recite that these ingredients are formulated with

"adjuvants" into the various forms including tablets, granules, suppositories, syrup and powder as recited in claim 5. "Adjuvant" is supported in the "Embodiment" on page 2 of the specification; and it is clear from the description that the active ingredients are formulated with adjuvants to provide the various forms of dosing.

Claim 5 is further amended to cancel "0.6 parts" and to recite the amount of primaquine is up to "0.2 parts" as is clearly supported near the bottom of page 1 of the specification.

Claim 6 is amended to recite a composition according to claim 5 wherein the amount of primaquine is 0.05 parts as supported in the specification in the "Embodiment" on page 2. This figure was discussed during the interview. As shown in the "Embodiment" the primaquine is 6/120 = 0.05 parts. It is noted that the ranges of ratios of claim 5 encompass the ratio of active ingredients employed in the human trials reported in the Rule 1.132 Supplemental Declaration; and the amounts of primaquine in claims 5 and 6 are commensurate in scope with the Declaration.

Claim 7 is amended to be dependent on claim 5 and is further amended to include the word "dose" as well as "tablets" since the "syrup," for example, is clearly provided in a "dose" which is not a tablet. Claim 8 is amended to be dependent on claim 6 and to similarly include "dose" as well as "tablets." These amendments are supported in the specification.

The above amendments are respectfully submitted to be supported by the originally filed specification and are in accord with the discussion between applicants' attorney and Examiner Arnold during the Interview. The amended claims are believed to fully comply with the Rules and Section 112 of the Statute for reasons stated.

Claim Rejections – 35 USC § 103

As discussed at the Interview, in line with the Examiner's comments in the Official Action of December 28, 2009, and as argued by applicants' attorney, the applicants' Supplemental Declaration demonstrates an unexpected shorter course of treatment with less side effects. As pointed out by the Examiner at page 10 of the Official Action, the primary reference, Giao employs a total dosage of 3576 mg over three days which is about double applicants'

dosage of1750 mg over a shorter period of time (paragraph 11 of the Supplemental Declaration). Giao's disclosure of the four way combination of dihydroartemisinin, piperaquine, trimethoprim and primaquine for the treatment of malaria clearly does not predict the shorter treatment and lower dosage invented by applicants which consists of the combination artemisinin, piperaquine and primaquine. Main claim 5 is further amended to recite that the composition "consists of" the three active ingredients that are formulated with adjuvants into the various forms of dosing thereby precluding, for example, the presence of Giao's trimethoprim. Applicants' claims are not obvious from the prior references taken alone or in any combination.

Additionally, dependent claims 7 and 8 are further patentably distinct in that the dose of primaquine is formulated into a separate tablet or dose to be taken along side the dose of the combined artemisinin and primaraquine.

For these reasons it is respectfully submitted that all claims as currently amended are patentable over the prior art and comply with Section 112 of the Statute; and are properly allowable.

Lack of *prima facie* obviousness of the amended claims

For the record, applicants further argue that the claims as amended are not *prima facie* obvious over the prior art taken alone or in any combination. The rejection applied in the current Official Action to which this paper is responsive is Giao in view of the EP Abstract and White, and Lai et al, and Klayman.

Giao et al. discloses a four way combination of dihydroartemisinin, piperaquine, trimethoprim and primaquine for the treatment of malaria. Applicants' revised composition claims are clearly and patentably distinguished over Giao et al since applicants' claims are now limited to artemisinin (not dihydroartemisinin), piperaquine, and primaquine plus formulation adjuvants. The phrase "consisting of" clearly excludes other active ingredients such as trimethoprim which is an essential ingredient of Giao et al's composition and present in Giao in relatively large ratios. The EP Abstract teaches combinations including the more potent dihydroartemisin and other derivatives with primaquine but fails to teach applicants' claimed composition which excludes dihydroartemisinin and other derivatives; and the reference fails to

include piperaquine. Lai et al pertains to cancer treatments and does not establish the functional equivalence of dihydroartemisinin in the treatment of malaria. In addition the teachings of Klayman show that dihydroartemisinin is a more potent derivate than artemisinin for malaria treatment. Hence, Klayman leads away from applicants' selection of artemisinin in a three way combination with primaraquine and a low dose of primaquine where the objective is to shorten the course of treatment and achieve reduced side effects.

Expressed in different words, Klayman would not motivate the person of ordinary skill in the art to employ artemisinin in place of the more potent derivative, dihydroartemisinin, and have a reasonable expectation of reducing the dosing treatment as described in the specification. In fact, one might expect the opposite effect. In addition, the effect of removal of trimethoprim from the Gaio et al treatment regimen renders the effect of applicants' new combination unpredictable. From the extract of data in Gaio et al, it should be noted that about 35 hours on average are required for treatment with Gaio's proposed trimethoprim containing formula while applicants' treatments may be accomplished in 24 hours.

The White reference (Phil Trans R Soc Lond B 1999, 354,739-749) clearly points out the importance of malaria treatments of low cost and ready availability and that malaria is the top parasitic infectious disease deserving great attention from the medical arts. However, White does not show or suggest the novel and unpredicted ratio of a composition consisting of artemisinin, primaraquine, and low dose of primaquine which applicants discovered and which leads to short, efficacious, less toxic, and less costly treatment of this dreaded disease. Moreover, none of the references show or suggest the contents of dependent claims 7 and 8.

The references in combination or alone clearly do not render applicants' amended claims unpatentable.

The Supreme Court's opinion in KSR teaches that while there is no rigid rule for determining motivation or suggestion in the prior art, reasonable predictability is still required based on the prior art. In a subsequent opinion in *Takeda v. Alphapharm,* 492. F. 3d1350 (Fed. Cir. 2007), the Federal Circuit holds that detailed and specific findings are required to support obviousness rejections and that generalizations are not sufficient. Applying those cases to the present situation, one would observe that none of the references alone or in combination point to

the applicants' empirical discovery of the claimed ratios employing artemisinin, instead of the more costly and thought to be more potent derivates thereof.

The Supplementary Declaration

In the prior Amendment and Response, applicants detailed the manner in which the Supplementary Declaration overcomes the prior art. Applicants further note with approval examiner's calculations and recognition of the unexpected results as applied to Giao at page 10 of the Official Action and as discussed above.

Conclusion

For the above stated reasons the amended claims are not obvious and fully comply with the Statutes and Rules. A notice of allowance is courteously solicited.

Applicants believe no fee is due with this response. However, if any fee is due, the USPTO is hereby authorized and requested to charge our Deposit Account No. 03-2775, under Order No. 13796-00002-US from which the undersigned is authorized to draw.

Examiner is requested to contact applicants' undersigned attorney as necessary.

Respectfully submitted,

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